19T

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/546,573	04/10/2000	Mads Holten-Andersen	19829-000300US	3408

7590 06/02/2004

STANISLAUS AKSMAN, ESQ
HUNTON & WILLIAMS
1900 K STREET NW SUITE 1200
WASHINGTON, DC 20006

EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 06/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/546,573	HOLTEN-ANDERSEN ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 5-9, 11-15, 19-23, 25-29, 34-36, and 39-54* is/are pending in the application.

4a) Of the above claim(s) *5-9,11,12,19-23,25,26,41-50,53 and 54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 13-15, 27-29, 34-36, 39, 40, 51, and 52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20020728*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *20040122* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 30, 2003 has been entered.

2. The amendment filed April 23, 2004 is acknowledged and has been entered. Claims 51-54 have been added.

Regarding the listing of claims set forth in the amendment, it is noted the status of claims 6-9, 11, 12, 20-23, 25, and 26 is not correctly indicated; claims 6-9, 11, 12, 20-23, 25, and 26 were withdrawn from further prosecution as of the Office action mailed November 9, 2001.

In order to expedite prosecution, and in lieu of mailing a notice of non-compliancy, Applicant is requested to submit in reply to this Office action, a listing of the claims correctly indicating the status of all claims, as required by 37 CFR § 1.121, as amended June 30, 2003.

For further explanation of the amendment format required by 37 CFR § 1.121, see MPEP § 714 and the USPTO website at:

http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/officeflyer.pdf.

3. The amendment filed July 16, 2003 is acknowledged and has been entered in part. Claims 4, 10, 18, 24, 30-33, and 38 have been canceled. Claims 1, 5-7, 9, 11, 13-15, 19-21, 25, 27, 28, 34, 39, and 40 have been amended. Claims 41-50 have been added.

Regarding the listing of claims set forth in the amendment filed July 16, 2003, it is noted that the status of claims 16 and 17 is not indicated; claims 16 and 17 were

canceled by the amendment filed March 11, 2002. Furthermore, the status of claims 6-9, 11, 12, 20-23, 25, and 26 is not correctly indicated; claims 6-9, 11, 12, 20-23, 25, and 26 were withdrawn from further prosecution as of the Office action mailed November 9, 2001.

4. Claims 1, 5-9, 11-15, 19-23, 25-29, 34-36, and 39-54 are pending in the application. Claims 5-9, 11, 12, 19-23, 25, 26, 41-50, 53, and 54 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the response filed June 5, 2001.

5. Claims 1, 13-15, 27-29, 34-36, 39, 40, 51, and 52 are currently under prosecution.

Election/Restrictions

6. Newly submitted claims 5, 19, 41-50, 53, and 54 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

Claims 43-50 are drawn to the subject matter of non-elected invention of Groups II and IV, as set forth in the Office action mailed April 5, 2001.

Claims 41 and 42 are drawn to a method for screening for colorectal or metastatic breast cancer, respectively, each method comprising determining a combination parameter of the concentration of total TIMP-1 with the concentration of free TIMP-1 in a plasma sample and indicating the individual is likely to have the cancer if the value of the combination parameter is at or beyond a discriminating value. Thus, the inventions of claims 41 and 42 are distinct from the elected invention, since the inventions of claims 41 and 42 comprise the use of a biomarker, which is represented by a combination parameter determined by measuring both the concentration of total TIMP-1 and the concentration of free TIMP-1 in a plasma sample, whereas the elected invention comprises the use of a different biomarker, which is represented by a parameter determined by measuring only the total concentration of TIMP-1 in a plasma

sample. Moreover, the inventions of claims 41 and 42 are distinct from the elected invention because the inventions of claims 41 and 42 comprise a process that is different from the process comprised by the elected invention; e.g., the inventions of claims 41 and 42 comprise a process that uses a discriminating value that differs from the discriminating value that is used in the process comprised by the elected invention. Because the parameters that are used as biomarkers differ, the search required to examine the inventions of claims 41 and 42 differs from the search required to examine the elected invention, such that searching and examining the additional inventions of claims 41 and 42 would constitute a serious burden. Claims 5 and 19 have been amended such that the claims depend from claims 41 and 42, respectively; therefore, claims 5 and 19 are presently grouped with the inventions of claims 41 and 42, respectively.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 5, 19, 41-50, 53, and 54 have been withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

7. At pages 14 and 15 of the amendment filed July 16, 2003, Applicant has continued to traverse the restriction and election requirement set forth in the Office action mailed April 5, 2001. Applicant's remarks have been carefully considered, but the restriction and election requirement was made FINAL in the Office action mailed November 9, 2001.

Information Disclosure Statement

8. The information disclosure filed June 28, 2002 has been considered. An initialed copy is enclosed.

At page 26, paragraph 5, of the amendment filed July 16, 2003, it is noted that Applicant has indicated an IDS is attached to the amendment filed July 16, 2003; however, an IDS attached to the amendment has not been received.

Grounds of Objection and Rejection Withdrawn

9. Unless specifically reiterated below, the grounds of objection and rejection set forth in the previous Office action mailed July 2, 2002 have been withdrawn. Applicant has provided an acceptable abstract and Applicant's amendments to the claims have rendered the grounds of non-reiterated rejections moot.

Claim Objections

10. Claims 13, 14, 51, and 52 are objected to because the claims are drawn in the alternative to the subject matter of non-elected inventions. Appropriate correction is required.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1, 13-15, 27-29, 34-36, 39, 40, 51, and 52 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Presently, claims 1, 13, 14, 28, 29, 34-36, 39, 40, 51, and 52 are drawn to a method for determining whether an individual is likely to have colorectal cancer. Claims 15, 27, and 34-36 are drawn to a method for determining whether a patient who has been treated for primary breast cancer is likely to have metastatic breast cancer.

The issues at hand have been greatly simplified during prosecution through multiple interviews. The central issue is that the claims are drawn to a method that comprises comparing the value of the total concentration of TIMP-1 in a plasma sample to "a discriminating value". Thus, to practice the claimed invention, the discriminating

value must be known or determined. Because determining the discriminating value, which can be used to discriminate an individual having colorectal cancer or metastatic breast cancer from an unaffected individual would require the practitioner to perform an undue amount of additional experimentation for the reasons already addressed in the previous Office action mailed July 2, 2002, the amount of guidance, direction, and exemplification disclosed in the specification is not sufficient to meet the enablement requirement set forth under 37 CFR § 112, first paragraph.

At pages 16-22 of the amendment filed July 16, 2003, Applicant has traversed the ground of rejection set forth in the previous Office action mailed July 2, 2002. However, the essence of Applicant's argument is, "the discriminating value can be easily determined by a clinician based on his or her choice of selectivity and specificity" (page 22, paragraph 2).

Applicant's arguments have been carefully considered but not found persuasive because the discriminating value that is to be used in practicing the claimed invention with any given predetermined sensitivity or predetermined specificity, such that the method can be used to successfully identify an individual likely to have colorectal cancer or malignant breast cancer, has not been disclosed. As reiterated in the subsequent Office action mailed July 2, 2002, because the range of the values of the concentrations of TIMP-1 in the bodily fluid of patients known to have cancer substantially overlaps the range of the values of the concentrations of TIMP-1 in the bodily fluid of individuals considered healthy and disease-free, the discriminatory value of the concentration of TIMP-1 in the bodily fluids, which might delineate one group from the other, is obscured. For example, the values of the concentration of TIMP-1 in patients previously diagnosed with colorectal cancer are disclosed as ranging from 53.7 to 788.7 micrograms/liter, but the values of the concentration of TIMP-1 in disease-free individuals are disclosed as ranging from 51.0 to 156.2 micrograms/liter. The substantial overlap in the ranges of the values of the TIMP-1 concentrations in the plasma of affected and unaffected individuals underscores a lack of predictability in practicing the claimed method to determine the likelihood that an individual is affected by colorectal cancer or malignant breast cancer; therefore, as first noted in the Office

action mailed November 9, 2001, Holten-Andersen et al. (*Clinical Cancer Research* **6**: 4292-4299, 2000) concludes: "Additional studies are needed to validate the clinical usefulness of plasma TIMP-1 measurements" (abstract). Accordingly, because the discriminating value must be determined before the invention can be used, and because determining the discriminating value would require the practitioner to perform an undue amount of additional experimentation, the amount of guidance, direction, and exemplification disclosed in the specification is not sufficient to meet the enablement requirement set forth under 37 CFR § 112, first paragraph.

In addition, as amended and clarified in reply to the previous Office action, claim 1 is drawn to a method for screening an individual for colorectal cancer, "whereby the likelihood that said individual has **or will have** colorectal cancer is determined" (emboldened for emphasis). Claim 15 is drawn to a method for screening an individual for metastatic breast cancer, "whereby the likelihood that said individual has **or will have** metastatic breast cancer is determined" (emboldened for emphasis). For reasons already of record, the amount of guidance, direction, and exemplification set forth in the specification would not be sufficient to enable the skilled artisan to use the claimed invention to determine the likelihood that an individual will have colorectal cancer. The concentration of TIMP-1 in plasma is associated with the presence of colorectal cancer or metastases of primary breast cancer, not with a predisposition to colorectal or malignant breast cancer. The skilled artisan would not accept the assertion that the claimed invention could be practiced successfully to predict whether a patient will develop colorectal cancer or malignant breast cancer, absent some showing that the TIMP-1 levels in plasma are associated with a predisposition to colorectal cancer or malignant breast cancer.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claim 1, 13-15, 27-29, 34-36, 39, 40, 51, and 52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 is indefinite because the claim recites, "wherein the individual is a member of an unselected population". If an individual were screened using the method of claim 1, the individual would be a member of a selected population; accordingly, it cannot be determined how the method can be practiced with a member of an unselected population. Therefore, the metes and bounds of the subject matter that Applicant regards as the invention cannot be determined.

Claims 1, 4, 5, 13-15, 18, 19, 27-36, and 38-40 are vague and indefinite because claims 1 and 15 recite the phrase "a discriminating value". For the reasons set forth in the previous Office action, the recitation of the phrase renders the claims vague and indefinite because discriminating value is not defined, such that the skilled artisan could determine the metes and bounds of the claimed invention.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

16. Claims 1, 15, 34, 35, 39, and 40 are rejected under 35 U.S.C. 102(a) as being anticipated by Holten-Andersen et al. (*Br. J. Cancer* **80**: 495-503, 1999; entire document).

Holten-Andersen et al. teaches the quantification of total TIMP-1 concentrations in plasma samples of individuals using an ELISA; see the entire document, particularly, e.g., the abstract; and page 496, columns 1 and 2. Holten-Andersen et al. teaches: "The mean level of TIMP-1 in EDTA plasma from 143 patients with Dukes' stage D

colorectal cancer was 240 ± 145 μg/l and a Mann-Whitney test demonstrated a highly significant difference between TIMP-1 levels in healthy blood donors and colorectal cancer patients" (see, e.g., the abstract). Holten-Andersen et al. teaches similar findings were obtained for patients with stage IV metastatic breast cancer; see, e.g., the abstract; and page 496, column 1. Therefore, Holten-Andersen et al. discloses, while normal donors were found to have low and very narrowly ranging plasma TIMP-1 concentrations, patients with advanced colorectal cancer or breast cancer present plasma TIMP-1 concentrations significantly elevated above those levels (see, e.g., page 496, column 1). Although Holten-Andersen et al. does not expressly teach whether the individuals having colorectal cancer had colon cancer or rectal cancer, the individuals had to have had either colon cancer or rectal cancer, or both.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. Claims 1, 14, 51, and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Holten-Andersen et al. (*Br. J. Cancer* **80**: 495-503, 1999; of record).

Holten-Andersen et al. teaches that which is set forth above, but does not expressly teach screening an individual that is a member of a population already identified as having an increased risk of developing colorectal cancer.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to use the method of Holten-Andersen et al. to screen an individual that is a member of a population already identified as having an increased risk of developing cancer. One of ordinary skill in the art would have been motivated to do so to screen the individual for the presence of colorectal cancer, since the individual was already identified to have an increased risk of developing the cancer.

Double Patenting

19. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

20. Claims 1, 13-15, 27-29, 34-36, 39, 40, 51, and 52 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 3, 13-17, 27-32, and 34-37 of copending Application No. 10/117,030. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant and copending claims are drawn to the same or nearly the same methods of screening an individual to determine if the individual has colorectal cancer or malignant breast cancer.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

21. Claims 1, 13-15, 27-29, 34-36, 39, 40, 51, and 52 are directed to an invention not patentably distinct from claims 1, 2, 3, 13-17, 27-32, and 34-37 of commonly assigned

US Application No. 10/117,030. Specifically, although the conflicting claims are not identical, they are not patentably distinct from each other for the reason addressed above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned US Application No. 10/117,030, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 35 U.S.C. 103(c) and 37 CFR 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

Conclusion

22. No claims are allowed.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
May 28, 2004

Phillip Gambel
PHILLIP GAMBEL, PH.D
PRIMARY EXAMINER
TECH CENTER 1600
6/1/04